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Device-guided breathing exercises for the treatment of hypertension

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Published in:
World Journal of Cardiology

DOI:
[10.4330/wjc.v6.i5.277](https://doi.org/10.4330/wjc.v6.i5.277)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2014

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

van Hateren, K. JJ., Landman, G. W., Logtenberg, S. J., Bilo, H. J., & Kleefstra, N. (2014). Device-guided breathing exercises for the treatment of hypertension: An overview. *World Journal of Cardiology*, 6(5), 277-282. <https://doi.org/10.4330/wjc.v6.i5.277>

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WJC 6th Anniversary Special Issues (1): Hypertension

Device-guided breathing exercises for the treatment of hypertension: An overview

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Received: November 22, 2013 Revised: February 14, 2014

Accepted: April 17, 2014

Published online: May 26, 2014

cial effects on blood pressure. There is only 1 study that used a sham device as a control group. All other studies were to some extent methodologically flawed. Based on the studies with an acceptable methodological quality, there is no clear evidence supporting a short-term beneficial effect on blood pressure by using device-guided breathing.

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Key words: Hypertension; Device-guided breathing; Review

Core tip: This review discusses all randomized controlled trials that have investigated the effects of device-guided breathing on blood pressure. There were 6 studies with an acceptable control group. Two (manufacturer sponsored) trials showed beneficial effects of device-guided breathing, both used listening to music as a control group. The remaining 4 studies observed no beneficial effects. We conclude that there is no sufficient evidence for recommending device-guided breathing in the treatment of hypertension.

Abstract

The American Heart Association considers device-guided breathing as a reasonable treatment modality in their statement on non-pharmacological options for lowering blood pressure. This review discusses all randomized controlled trials that have investigated the effects of device-guided breathing on blood pressure in patients with hypertension. Thirteen studies were included in this review. In total, 627 patients were included, of which 365 patients were allocated to device-guided breathing. Only 6 studies used acceptable control groups: listening to music, meditative relaxation exercises, or a sham-device. Two sponsored trials showed beneficial effects of device-guided breathing, both used listening to music as a control group. The remaining 4 studies, which had no employees of the manufacturer listed as co-author, observed no benefi-

van Hateren KJ, Landman GW, Logtenberg SJ, Bilo HJ, Kleefstra N. Device-guided breathing exercises for the treatment of hypertension: An overview. *World J Cardiol* 2014; 6(5): 277-282 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v6/i5/277.htm> DOI: <http://dx.doi.org/10.4330/wjc.v6.i5.277>

INTRODUCTION

Treatment of hypertension includes both pharmacological and non-pharmacological interventions. Accepted non-pharmacological interventions are sodium restriction, losing weight, increasing physical activity, smoking cessation and optimizing alcohol consumption^[1-3]. In a scientific statement from the American Heart Associa-

tion (AHA) regarding non-pharmacological options for lowering blood pressure, device-guided slow breathing is described as a reasonable treatment modality to reduce blood pressure (Class II A, Level of Evidence B)^[4]. Device-guided slow breathing aims at lowering the respiratory frequency into a so-called “therapeutic breathing zone” (less than 10 breaths per minute) through biofeedback by using an electronic device. Exercises are regarded as successful if the total exercise time is at least 45 min per week, preferably 15 min daily^[4]. Sympathetic overactivity is hypothesized as an important contributing factor in the development of hypertension^[5-7]. Efforts aimed at reducing this autonomic imbalance may indeed be an effective therapy for hypertension. Slow and regular breathing, guided by musical tones, will lead to a reduction of sympathetic activity and also to an increase in heart rate variability^[5]. The baroreceptors measure blood pressure in the carotid arteries and the aorta, and an increase in pressure leads to parasympathetic activation and vice versa (negative feedback mechanism). As an increase in heart rate variability will lead to an increased baroreflex sensitivity^[5], device-guided breathing may lead to lower blood pressure values.

The conclusions of the writing group of the AHA statement were based on a meta-analysis^[8] and several other studies^[9-19]. After the publication of the guideline, two additional studies have been published^[20,21]. The overall effect estimate in the meta-analysis showed a small beneficial blood pressure lowering effect [a reduction of 3.7 mmHg in systolic blood pressure (SBP)], but the authors of the meta-analysis stated that the results of the overall effect estimates should be interpreted with caution because of methodological flaws in most studies. Beneficial effects were not observed after excluding studies with high risk of bias or studies that were sponsored by or involved the manufacturer of the device^[8]. A previous editorial already emphasized that an independent double-blind study with a proper control group, preferably a sham device, would be necessary to answer the question whether device-guided breathing has any effect on blood pressure^[22]. Recently, an investigator-initiated double-blind and sham-controlled trial was performed^[20]. This review discusses all randomized controlled trials (RCTs) that have investigated the effects of device-guided breathing on blood pressure in patients with hypertension.

PREVIOUS STUDIES

Thirteen studies, of which the study and patient characteristics are presented in Table 1, were included in this review. In total, 627 patients were included, of which 365 patients were allocated to device-guided breathing. Except for 1 study in which a bi-level positive pressure device (BiPAP®) was used^[19], all other studies used the Resperate® device. The Resperate® device uses a form of biofeedback with “breathe in” and “breathe out” instructions according to the listeners breathing rate to guide the respiration into a lower frequency by prolong-

ing expiration. The BiPAP® device was used for the treatment of patients with obstructive sleep apnea and it was also capable of guiding patients’ respiratory rate to less than 10 breaths per minute. Three studies had no control group^[11,12,19], 4 studies compared the intervention to usual care or frequent blood pressure measurements^[13,14,17,21], 4 studies compared the intervention to listening to music^[9,10,15,16], 1 study compared the intervention to meditative relaxation exercises^[18], and 1 study used a sham-device in the control group^[20]. Except for 3 studies^[15,16,20], all other studies were sponsored by or involved the manufacturer of the Resperate® and BiPAP® devices. According to the meta-analysis by Mahtani *et al*^[8], the Anderson paper was also not sponsored by the manufacturer^[18]. However, the acknowledgements section of this manuscript states that Drs. B. Gavish, an employee of the company that manufactures the Resperate® device, had reviewed the paper.

EFFECTS OF DEVICE-GUIDED BREATHING

Table 1 presents an overview of the effects of device-guided breathing on blood pressure. Only 4 studies reported between-group-differences including the 95% confidence intervals^[9,15,16,20]. Significant decreases in blood pressure were observed in all 3 studies without a control group^[11,12,19]. A significant between-group-difference was observed in 2 out of 4 studies that compared device-guided breathing to daily blood pressure measurements^[13], and usual care^[17]. Studies comparing device-guided breathing to usual care cannot differentiate the 3 possible mechanisms through which the Resperate® could have a blood pressure lowering effect: (1) effects of guided slowing of breathing itself; (2) listening to music; and (3) sitting still. Conclusions regarding the isolated effect of device-guided breathing are only valid when a study has an appropriate control group to disentangle these 3 effects. Therefore, this review will further focus on the 6 studies that used acceptable control groups: listening to music, meditative relaxation exercises and a sham-device^[9,10,15,16,18,20]. Two sponsored trials showed beneficial effects of device-guided breathing, both used listening to music as a control group^[9,10]. In the study by Schein *et al*^[9] device-guided breathing was not effective in lowering SBP compared to the control group. This study pre-defined a 5 mmHg reduction in diastolic blood pressure (DBP) as clinically relevant. The difference in DBP change between both groups was 4.4 mmHg in favour of the intervention group ($P = 0.008$). Although a second study failed to predefine a clinically relevant difference, it showed a significant decrease in office SBP compared to a Walkman group (between-group-difference 4.6 mm Hg, $P = 0.001$)^[10]. The remaining 4 studies, which had no employees of the manufacturer listed as co-author, observed no beneficial effects on blood pressure^[15,16,18,20]. Only the study by Landman *et al*^[20] described the presence of 2 negative side-effects, but this was insufficient to conclude

Table 1 Study and patients characteristics

Ref.	Study group		Period (wk)	Study arm		Endpoint	Results (mean)		
	Disease, therapy, patients	Number (I/C)		Intervention	Control		Intervention (mmHg)	Control (mmHg)	Difference intervention vs control (mmHg)
Schein <i>et al</i> ^[9] , 2001; Israel	HT, medication, BP \geq 140/90, 25-75 yr	32/33	8	Resperate® 10 min/d	Walkman 10 min/d	SBP	156.6 > 141.4	154.7 > 143.4	-2.9 (-2.8-10.6)
						DBP	96.7 > 86.7 ^a	93.4 > 87.8	-4.4 ^a (1.1-7.6)
						Clinic, SBP	160 > 152.5	155 > 152.1	-4.6 ^a
						DBP	95 > 91	94 > 92.5	-2.5
Grossman <i>et al</i> ^[10] , 2001; Israel	HT, medication, BP \geq 140/90, 25-75 yr	18/15	8	Resperate® 10 min/d	Walkman 10 min/d	Home, SBP	157 > 152.0	151 > 149.8	-3.8
						DBP	94 > 91.3	90 > 90.9	-3.6 ^a
						24 h, SBP	137.1 > 129.9 ^a	-	-
						DBP	82.5 > 80.2	-	-
Rosenthal <i>et al</i> ^[11] , 2001; Israel	HT, medication, BP 130/85-180/110, 25-75 yr	13/-	8	Resperate® 15 min/d	-	SBP	137.1 > 129.9 ^a	-	-
						DBP	82.5 > 80.2	-	-
Viskoper <i>et al</i> ^[12] , 2003; Israel	HT, medication, SBP 140-160 or DBP 90-100, 40-80 yr	17/-	8	Resperate® 15 min/d	-	Home, SBP	156.4 > 150.0 ^a	-	-
						DBP	88.5 > 85.9 ^a	-	-
						Clinic, SBP	155.4 > 142.5 ^a	-	-
						DBP	88.9 > 82.0 ^a	-	-
Meles <i>et al</i> ^[13] , 2004; Italy	HT, 40-75 yr + 1) not treated, SBP 140-159 or DBP 90-99; OR = 2) medication and BP > 140/90	48/31	8	Resperate® 15 min/d	BP 1/d	Home, SBP	137 > 131.6 ^a	126 > 124.1	-3.5 ^a
						DBP	83 > 79.8 ^a	79 > 78.0	-2.2 ^a
						Clinic, SBP	141.4 > 135.9	133.2 > 133.0	-5.3
						DBP	88.1 > 84.5 ^a	85.9 > 86.8	-4.5 ^a
Elliot <i>et al</i> ^[14] , 2004; United States	HT, medication, SBP 140-179, DBP < 110, 40-75 yr	89/60	8	Resperate® 15 min/d	BP 3/d	Clinic, SBP	150.3 > 139.7	149.8 > 140.6	-1.4
						DBP	84.7 > 81.5	86.8 > 83.6	0.0
						Home, SBP	145.8 > 145.3	141.3 > 141.9	-1.1
						DBP	85.9 > 85.3	83.7 > 83.5	-0.4
Logtenberg <i>et al</i> ^[15] , 2007; The Netherlands	T2DM, HT, medication, SBP 140-160, > 18 yr	15/15	8	Resperate® 15 min/d	Discman 15 min/d	Clinic, SBP	153.5 > 146.0	150.4 > 138.2	4.7 (-11.7-2.3)
						DBP	83.0 > 82.0	87.0 > 81.5	4.6 (-10.4-2.3)
						Home, SBP	-	-	1.0 (-7.8-5.8)
						DBP	-	-	1.3 (-5.8-3.2)
Altena <i>et al</i> ^[16] , 2008; The Netherlands	HT, medication SBP 140-160, > 18 yr	15/15	8	Resperate® 15 min/d	Discman 15 min/d	Clinic, SBP	-9.8	-5.6	-4.2 (-12.4-3.9)
						DBP	-4.6	-2.0	-2.6 (-8.4-3.3)
						Home, SBP	-2.5	-2.9	0.5 (-3.7-4.8)
						DBP	-4.9	-3.4	-1.8 (-8.4-4.8)
Schein <i>et al</i> ^[17] , 2009; Israel	T2DM, HT, medication, SBP > 130	33/33	8	Resperate® 15 min/d	Usual care	Clinic, SBP	150 > 140	147 > 149	-12 ^a
						DBP	81 > 77	81 > 80	-3
						Clinic, SBP	141.8 > ?	140.1 > ?	-
						DBP	88.2 > ?	85.2 > ?	-
Anderson <i>et al</i> ^[18] , 2010; United States	Stage 1 HT or pre-hypertension, no medication, no CVD or T2DM.	20/20	4	Resperate® 15 min/d	Meditative exercise 15 min/d	24h, SBP	138.2 > 137.7	137.3 > 137.8	-1
						DBP	84.6 > 83.8	80.4 > 81.8	-2.2
						Clinic, SBP	140 > 130.4 ^a	-	-
						DBP	82.7 > 80.2	-	-
Bertisch <i>et al</i> ^[19] , 2011; United States	HT and OSA, medication or untreated, BP 120/80-160/100, 20-75 yr	25/-	8	BiPAP® 15 min/d	-	Clinic, SBP	140 > 130.4 ^a	-	-
						DBP	82.7 > 80.2	-	-
						Clinic, SBP	151.6 > 145.6	151.2 > 142.8	2.4 (-6.5-11.2)
						DBP	82.1 > 76.2	80.7 > 77.0	-2.3 (-6.7-2.2)
Landman <i>et al</i> ^[20] , 2013; The Netherlands	T2DM, HT, medication, SBP 140-160, \geq 18 yr	24/24	8	Resperate® 15 min/d	Sham-Device 15 min/d	Home, SBP	?	?	-3.0 (-13.2-7.2)
						DBP	?	?	0.1 (-6.9-7.1)
						24h, SBP	126.1 > 123.2 ^a	?	?
						DBP	?	?	?
Howorka <i>et al</i> ^[21] , 2013; Austria	T2DM, HT, medication, BP < target value, 18-78 yr	16/16	8	Resperate® 12 min/d	Usual care	Daytime SBP	129.3 > 127.1	?	?
						DBP	?	?	?
						Daytime SBP	129.3 > 127.1	?	?
						DBP	?	?	?

^a $P < 0.05$ vs control. I: Intervention; C: Control; HT: Hypertension; SBP: (Systolic) blood pressure; DBP: Diastolic blood pressure; T2DM: Type 2 diabetes mellitus; CVD: Cardiovascular disease; OSA: Obstructive sleep apnea.

that there was a causal relationship with device-guided breathing.

METHODOLOGICAL QUALITY

In order to compare the studies, we assessed the methodological quality using the criteria as described by van Tulder *et al*^[23] (Table 2). The quality of the study by An-

derson *et al.* was low; they used an open randomisation procedure without any further explanation regarding this procedure and blinding^[18]. After carefully evaluating the studies by Schein *et al*^[9] and Grossman *et al*^[10] several methodological questions remained unanswered. It was stated in the Schein *et al*^[9] study that the study had a double-blind study design^[9]. Randomisation was performed by a third party and a special technician delivered and

Table 2 Randomized controlled trials with an active control group: methodological quality

Criteria	Schein ^[9]	Grossman ^[10]	Logtenberg ^[15]	Altena ^[16]	Anderson ^[18]	Landman ^[20]
Randomization adequate	+/-	+	+	+	-	+
Treatment allocation concealed	+	?	+	+	-	+
Groups similar at baseline	+	+	+	+	+	+
Patient blinded	+/-	+/-	+	+	-	+
Care provider blinded	+/-	+/-	-	-	-	+
Outcome assessor blinded	-	?	-	-	-	+
Co-interventions avoided	+	+/-	?	+	?	+
Compliance acceptable	+	?	+	+	+	+
Withdrawal/drop-out rate acceptable	+	+	+	+	+	+
Timing of outcome assessment similar	+	+	+	+	+	+
Intention to treat analyses	+/-	+	+	+	-	+

explained the device and study procedures. Although the doctor was not aware of the group assignment, patients had weekly follow-up meetings including blood pressure measurements by that same person. Patients were requested not to talk about the specific device with their doctor or to other persons who may be participating in the study. As the patients saw their doctor very regularly it is not unlikely that the doctor became aware of group assignment. Therefore, from a methodological point of view, the authors could have opted for another person performing the outcome measurements. An alternative method would have been to check the success of the blinding procedure. The authors did not explain their rationale behind this randomisation procedure. Furthermore, there were several primary endpoints instead of 1 primary endpoint and 2 secondary endpoints. Also, 5% of all blood pressure data were excluded in an unconventional and post-hoc defined 'end of treatment period' analysis.

Grossman *et al*^[10] did not describe whether treatment allocation was concealed and who performed the outcome measurements. Also, data on compliance and whether the blinding procedure was a success, were not provided. Two patients in the control group started lifestyle modification programmes, but analyses without these patients did not change the results.

The Logtenberg, Altena *et al*^[16] and Landman *et al*^[20] studies have one important limitation in common: the width of the 95%CI of the change of office-measured SBP between groups^[15,16,20]. These studies were powered to detect an absolute reduction of 10 mmHg in SBP. In all these studies the limits of the confidence intervals exceeded the boundary of 10 mmHg. The 95%CI in the Logtenberg *et al*^[15] and Landman *et al*^[20] studies ranged from -2.3 mmHg to 11.7 mmHg, and -6.5 mmHg to 11.2 mmHg, respectively, with a direction in favour of the control group^[15,20]. This means that clinically relevant disadvantageous effects of device-guided breathing could not be ruled out. For the Altena *et al*^[16] study, the confidence interval ranged from -12.4 mmHg to 3.9 mmHg with a direction in favour of the intervention group^[16]. Logtenberg *et al*^[15] did not provide data on avoiding co-interventions, whereas Altena *et al*^[16] reported that 1 patient in the control group had a change in antihypertensive therapy (per-protocol analyses showing the same results).

HbA1c level was higher in the intervention group of the Landman *et al*^[20] study, but additional analyses in which adjustments for age, gender, body mass index and HbA1c were done did not relevantly change the results^[20]. The adjusted differences in SBP and DBP were 1.1 mmHg (95%CI: -7.6-9.8, in favour of the control group) and 3.5 mmHg (95%CI: -0.4-7.4, in favour of the intervention group), respectively. Finally, the Logtenberg *et al*^[15] and Altena *et al*^[16] studies had a single-blind design.

Sample size calculations were described in 4 studies^[9,15,16,20], and lacking in the Anderson *et al*^[18] and Grossman *et al*^[10] studies^[10,18]. Although Grossman *et al*^[10] mentioned that the group size was large enough, they didn't provide a calculation^[10]. The Logtenberg study based the calculation on mean SBP and standard deviation (SD) in their clinic^[15]. Altena *et al*^[16] used the mean blood pressure and SD that were observed in the Logtenberg *et al*^[15] study. The most conservative and optimal calculation was performed in the Landman study, as they based their sample size on the highest SD of the change in SBP in the Logtenberg *et al*^[15] (SD 9.4 mmHg) and Altena *et al*^[16] (SD 10.9 mmHg) studies^[20]. Comparable to their data analysis, Schein *et al*^[9] used an unconventional method for the estimation of their sample size. The standardised detectable difference was based on a previous study^[24] while they could have used the change in blood pressure and its SD.

DISCUSSION

Out of the 13 RCTs published, there were only a few studies with an acceptable methodological quality. All studies had a short follow-up period. In order to exert effects on cardiovascular morbidity by using device-guided breathing, the device has to be used for many months and preferably years. None of the studies investigated whether the device could be used for prolonged periods. There is 1 meta-analysis, without any involvement of the manufacturer, that showed a small beneficial effect on blood pressure with unclear clinical relevancy of using device guided breathing^[8]. As was discussed by the authors of this meta-analysis, the overall effect estimate could have been biased due to inclusion of inadequately controlled trials and sponsored studies. In studies with

an acceptable methodological quality, no beneficial effects were seen. Sensitivity analysis showed that studies, performed without involvement of the manufacturer, showed no beneficial effects of device-guided breathing^[8]. Since the meta-analysis was published, 1 additional study has been completed. This study, which had a successful double-blinding procedure and a sham control group, showed no beneficial effects and even possible adverse events^[20]. Unfortunately, the writing group of the AHA guideline on non-pharmacological hypertension treatment finished writing the guideline before publication of this latest trial. As this latest study has the highest level of evidence, the writing group from the AHA was asked to reconsider their recommendation from Class II A, Level of Evidence B into class III, Level of Evidence B (evidence that treatment is not effective)^[25]. The committee responded that they didn't believe that the recommendation should be changed^[26]. Despite the fact that the latest study showed possible adverse events, the writing group focussed on a small positive general effect estimate from the meta-analysis by Mahtani *et al*^[8] and a meta-analysis that was performed by themselves^[4]. This positive recommendation by the guideline committee does not seem to be in line with the evaluation of the authors of the Mahtani *et al*^[8] study who criticized the methodological quality of most studies and the sponsor involvement in the discussion section of that paper^[8]. Since 1 member, who was involved in evaluating the topic of device-guided breathing for the AHA guideline, previously received funding from the manufacturer of the Resperate® device, the response of the AHA guideline committee is of potential concern^[4]. We agree with Mahtani *et al*^[8] that there is a real possibility that bias was introduced in the overall effect estimate from combining not adequately controlled studies and by including studies with a high level of sponsor involvement.

CONCLUSION

We conclude that, based on studies with acceptable methodological quality, there is no evidence for a short-term beneficial effect on blood pressure by using device-guided breathing. A meta-analysis of individual patient data combining studies with adequate control groups should be performed in the near future. Since there are no trials, not even uncontrolled, with sufficient follow-up on the feasibility and safety of using the device for many months or years, this device cannot safely be advised for treating hypertension in daily practice.

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P- Reviewers: Kettering K, Manendra C, Petix NR, Sakabe K, Yves D **S- Editor:** Qi Y **L- Editor:** A **E- Editor:** Wu HL





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